DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/22/11 has been entered.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 10/7/11 has been considered by the examiner.

Status of Claims

Claims 1-15 and 17-26 are pending in this application. Claim 16 is cancelled. Claim 26 is newly added. Claims 1-7, 24, and 25 are withdrawn from consideration as being directed to a nonelected invention.

Claims 8-15, 17-23 and 26 are examined in this Office Action.

Status of Rejections

1. The rejection of claims 8, 9, 11, 15, and 23 under 35 U.S.C. 102(b) as being anticipated by US 2002/0142413 (Publication date: 10/03/2002) ['413] publication is withdrawn.

2. The rejection of claims 8-11, 13, 15 and 17-23 under 35 U.S.C. 103(a) as being unpatentable over Isotis (WO 02/060508 (cited on the 06/05/2009 IDS)) [Isotis], Brosnahan (USPN 6,149,688 (cited the 09/08/2009 office action)) [Brosnahan] and Phipps (USPN 6,063,894 (cited in the 09/08/2009 office action)) [Phipps] is withdrawn.

3. The rejection of claims 8 to 11, 13, 15 and 17-23 under 35 U.S.C. 103(a) as being unpatentable over Isotis, Brosnahan and Phipps and further in view of

Shikinami (US 2004/0258732) [Shikinami] and Hossainy (USPN 6,712,845) [Hossainy] is withdrawn.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 8-13, 15, 17-23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isotis (WO 02/060508 (cited on the 06/05/2009 IDS)) [Isotis], Brosnahan (USPN 6,149,688 (cited the 09/08/2009 office action)) [Brosnahan], Phipps

(USPN 6,063,894 (cited in the 09/08/2009 office action)) [Phipps] and Agrawal et al (US 6,255,359) [Agrawal].

Isotis discloses a method of preparing a porous scaffold for use in tissue engineering (abstract) wherein at least two polymers are blended in a low temperature mill (page 6, lines 24-25) to a size of 10-1000 um (page 8, line 8), the scaffold is formed under pressure (page 9, lines 3-5), and a solvent is used to dissolve the soluble particle (page 14, claim 3) (i.e. leaching) wherein the soluble particles comprise a polymer, PMMA (Isotis claim 3) that will dissolve without affecting the copolymer (Isotis claim 1) and thus at least two of the polymers have a different biodegradability (claims 8, 9, 11, 13, 15, 18 and 23).

Isotis differs from the claims in that the document fails to disclose a porosity gradient which increases from the core to the surface. However, Brosnahan, Phipps and Agrawal cure the deficiency.

Brosnahan discloses a bone implant with a porosity gradient with a dense core and a porous surface form by the removal of a binder (column 4, lines 47-57).

Phipps discloses the extraction of a soluble compound (column 4, lines 19-27) at 15 to 100 KHz (column 6, lines 34-37) and a temperature of 35 - 180°C (Phipps claim 19). These ranges overlap and make obvious the instantly claimed ranges. Further, Phipps discloses a working example wherein the ultrasound was performed for 60 minutes (example 11).

Agrawal discloses compositions comprising variable permeability and/or porosity and objects made therefrom (Abstract). Agrawal discloses the composition is density developed resulting in a variable concentration in pore-forming agent throughout the mixture through application of an external force on the mixture with or without continued agitation (Abstract). Agrawal discloses the pore-forming agent is then leached from the mixture to form a polymer matrix having variable permeability and/or porosity (Abstract). In particular, Agrawal discloses the mixing step can be the agitation step where the composition is mixed by vibronic agitation (col 2, line 66 to col 3, line 2). Agrawal discloses that force development (anisotropic distributions of particles in the polymer matrix caused by the application of an external applied force) of the composition is

preferably continued until a desired degree of variation in porosity and/or permeability is achieved (col 3, lines 3-7). Agrawal discloses formation of concentration gradients of pores (col 6, lines 26-28).

Agrawal discloses the compositions are first mixed and then subject to vibronic agitation to augment pore size and shape in the composition. Agrawal discloses anisotropic particle distributions can be induced in the composition either through the application of an external force or through the application of vibronic agitation (ultrasonic) or both (col 4, lines 3-24). Agrawal discloses the action of the applied external force in conjunction with agitation causes the agents to migrate in the composition based on their density (col 4, lines 3-24). Agrawal discloses the denser particles and more regular shaped particles tend to migrate faster than less dense particles and smaller and irregular shaped particles resulting in anisotropic distributions of pores, pore sizes and pore shapes throughout the composition (col 4, lines 3-24). Agrawal discloses that for vibronic agitation such as ultrasonic or mechanical vibratory excitation, the amplitude, direction and frequency of the agitation can affect particle distribution and the size and/or shape of a cavity produced in the polymer matrix during agitation (col 4, lines 3-24). Agrawal Figures 1-4 disclose formation of more pores at the surface than at the interior, thus teaching leaching of a first polymer to a greater extent at the surface and to a lesser extent at a core (ie figure 3b).

Agrawal discloses leaching ("selectively melted") by sonic methods (col 12, lines 53-65) and shaking the vessel to enhance leaching (col 14, lines 24-27), thus disclosing the claimed "leaching ..in an ultrasonic bath".

Agrawal discloses (col 15, lines 34-40) that where the implant is employed for the purpose of tissue regeneration, as for example, to promote guided tissue regeneration of periodontal tissue, it is preferred that the diameter of the pores in the matrix be effective to deter growth of epithelial cells into the polymer matrix of the implant and enhance growth of connective tissue cells into the matrix.

It would have been obvious to one of ordinary skill in the art to provide two polymers in a copolymers form and provide a sacrificial polymer to form pores from particulates by cryogenic milling, compression and molding, and leaching the sacrificial

polymer as taught by Isotis and provide a porosity gradient as taught by Agrawal in view of the teachings of Brosnahan teaching an implant having a porosity which allows bone tissue ingrowth for repair (column 2, lines 44-48 and column 4, lines 57-58), Agrawal disclosing the importance of pore size in tissue regeneration and Phipps disclosing the enhancement of mechanical properties of the polymer by leaching compounds in an ultrasonic bath ('894, column 4, lines 19-27). One of ordinary skill would have been motivated to modify the Isotis implant in order to obtain and achieve the advantages taught by Brosnahan (porosity allowing ingrowth), Agrawal (importance of pore size in tissue regeneration) and Phipps (enhancement of mechanical properties).

Regarding claims 8 and 22, Brosnahan discloses a bone implant with a porosity gradient with a dense core and a porous surface form by the removal of a binder (column 4, lines 47-57). Agrawal discloses (Figures 1-4) formation of more pores at the surface than at the interior, thus teaching leaching of a first polymer to a greater extent at the surface and to a lesser extent at a core (ie figure 3b). It would have been obvious to one of ordinary skill that the method of implant formation taught by Agrawal would be applicable to any tissue, such as bone, for which an implant was desired in view of the ability to design the implant to have the necessary tissue compatibility.

Regarding claims 10 and 11, Isotis discloses a polymer ratio of 60:40 to 30:70 (page 4) of aromatic polyesters and polyalkylene glycol terephthalate and polybutylene terephthalate (page 4, lines 1-6; page 5, lines 13-17; and page 6, lines 1-3).

Regarding claim 12, Agrawal discloses the solvent can be an alcohol (col 11, line 45).

Regarding claims 19-21, because Isotis discloses the same particle size as the particle size in the instant application, it would be obvious to one of ordinary skill in the art to adjust the settings to optimize the particle size.

Regarding claim 17, Phipps discloses the extraction of a soluble compound ('894, column 4, lines 19-27) at 15 to 100 KHz ('894, column 6, lines 34-37) and a temperature of 35 - 180°C (column 18). These ranges overlap and make obvious the instantly claimed ranges. Further, Phipps discloses a working example wherein the ultrasound was performed for 60 minutes (example 11).

Regarding claim 26, one of ordinary skill would have been able to determine the amount of time necessary to remove any or all of the first polymer in order to obtain a scaffold having a desired degree of porosity, lacking evidence to the contrary. Brosnahan discloses a bone implant with a porosity gradient with a dense core and a porous surface form by the removal of a binder (column 4, lines 47-57) (claims 8 and 22). Agrawal discloses that for vibronic agitation such as ultrasonic or mechanical vibratory excitation, the amplitude, direction and frequency of the agitation can affect particle distribution and the size and/or shape of a cavity produced in the polymer matrix during agitation (col 4, lines 3-24). Agrawal Figures 1-4 disclose formation of more pores at the surface than at the interior, thus teaching leaching of a first polymer to a greater extent at the surface and to a lesser extent at a core (ie figure 3b).

All the claimed elements herein are known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

In light of the foregoing discussion, the claimed subject matter would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of skill in the art at the time the claimed invention was made, as evidenced by the references.

2. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Isotis [Isotis], Brosnahan [Brosnahan], [Phipps] and Agrawal as applied to claims 8-13, 15 and 18-23 above and further in view of Shikinami [Shikinami] and Hossainy [Hossainy]. The teachings of Isotis, Brosnahan, Phipps and Agrawal above are incorporated herein in their entirety.

Isotis, Brosnahan, Phipps and Agrawal differ from the claims in that the documents fail to disclose the compression molding conditions. However, Shikinami and Hossainy cure the deficiency.

Shikinami discloses a porous, copolymeric implant material comprising a porous block copolymer [0022] formed by compression molding at about 70°C [0050] and a compression strength of approximately 1MPa to 5 MPa [0058]. Shikinami discloses values overlapping the claimed ranges of 0 to 20 Mpa and temperatures of 25 C to 80 C (claims 12 and 14),

Hossainy discloses the removal of one polymer from a coating comprising at least two polymers and provides an embodiment where the process may be repeated (column 8, line 49 to column 9, line 40) using solvents such as acetone, chloroform, and other (column 3, lines 44-55) (claim 12).

It would have been obvious to one of ordinary skill to cryogenically mill, compress, and leach a sacrificial polymer from a composition in an ultrasonic bath with at least two polymers as taught by Isotis, Brosnahan, Phipps and Agrawal and to compression mold with the parameters as taught by Shikinami and Hossainy. One of ordinary skill in the art would have been motivated to utilize the molding parameters in view of Shikinami, disclosing a porous polymeric material used for bone tissue regeneration or artificial cartilage and various other clinical applications (page 4, paragraphs 22, 23, and 30) and that compression molding can be used to control the pore size in a structure (page 7, paragraph 61) and Hossainy disclosing a method of using solvents to remove a polymer from a copolymeric surface (column 2, lines 8-14 and column 5, lines 17- 22).

One of ordinary skill would have been motivated to design an implant having the desired degree of porosity to match the tissue site of use in order to optimize therapeutic outcome for the patient.

In light of the foregoing discussion, the claimed subject matter would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, in the absence of evidence to

the contrary, the invention as a whole would have been prima facie obvious to one of skill in the art at the time the claimed invention was made, as evidenced by the references.

Response to Arguments

Applicants' arguments, filed 6/22/10, have been considered but not found persuasive.

1. Applicants' arguments are moot in view of the withdrawal of the rejection under 35 USC 102(b) over Brady.

2. Applicants argue (pages 8-10) that Isotis teaches away from controlled differential leaching of a first polymer at the surface and core and that Isotis does not disclose or suggest ultrasonic leaching or controlled differential leaching.

In reply, Brosnahan, not Isotis, is cited for teaching porosity gradients. Brosnahan discloses a bone implant with a porosity gradient with a dense core and a porous surface form by the removal of a binder (column 4, lines 47-57). Applicants are arguing the references individually and not the combination. Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references. In re Merck, 800 F.2d 1091 (Fed. Cir. 1986); In re Keller, 642 F.2d 413 (C.C.P.A. 1981) (A rejection premised upon a combination of references cannot be overcome by attacking the references individually). Further, Agrawal is newly cited for teaching methods of leaching (using ultrasonic vibration) to obtain gradients in porosity.

3. Applicants argue that

> The Examiner additionally alleges in the last full paragraph on page 6 of the Office Action that "wherein leaching of the first polymer is controlled so that removal of the first polymer occurs to a greater extent at a surface of the scaffold, and to a lesser extent at a core of the scaffold" is inherent in Isotis per standard physical chemistry.

In reply, porosity occurs from the outside to the inside of the implant as taught by Brosnahan, disclosing obtaining a bone implant with a porosity gradient with a dense core and a porous surface form by the removal of a binder (column 4, lines 47-57). Further, Agrawal is newly cited for teaching methods of leaching (using ultrasonic vibration) to obtain gradients in porosity. Agrawal discloses implants having the claimed greater porosity at the surface and less porosity at the core.

Applicants are arguing the references individually and not the combination. Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references. In re Merck, 800 F.2d 1091 (Fed. Cir. 1986); In re Keller, 642 F.2d 413 (C.C.P.A. 1981) (A rejection premised upon a combination of references cannot be overcome by attacking the references individually).

4. Applicants argue

> Rather, this paragraph merely teaches that the initial amount and dimensions of polymer powder and soluble particles used, respectfully, can be initially controlled during blending to ultimately affect pore size and distribution. Isotis does not describe controlling leaching after blending "so that removal of the first polymer occurs to a greater extent at a surface of the scaffold, and to a lesser extent at a core of the scaffold" as required in independent claim 8. Thus, it is submitted that one of ordinary skill in the art would not have found motivation to for the proposed modification in Isotis.

In reply, Applicants are again arguing the references individually and not the combination. Brosnahan, not Isotis, is cited for disclosing porosity gradients. Agrawal is newly cited for teaching methods of leaching (using ultrasonic vibration) to obtain gradients in porosity. Agrawal discloses implants having the claimed greater porosity at the surface and less porosity at the core.

5. Applicants argue

> Secondly, while Brosnahan describes an artificial bone graft implant with a porosity gradient at column 4, lines 52-56, the porosity gradient is not

> created by controlled leaching. Rather, it is only mentioned at column 4, lines 49-50 that a different porosity of the core and shell is obtained by burning out during sintering. Indeed, Brosnahan fails to disclose any teaching on how the pore gradient at column 4, lines 52-56 is manufactured. Accordingly, it is not apparent how the mention of a process of burning out binder during sintering can provide any further insight in how to control leaching of the first polymer "so that removal of the first polymer occurs to a greater extent at a surface of the scaffold, and to a lesser extent at a core of the scaffold" as required in independent claim 8. Thus, it is submitted that one of ordinary skill in the art would not have found motivation to for the proposed modification in Brosnahan.

In reply, Applicants' method relies on a solvent that reacts with only a first of the polymers but not the other polymers or has limited or slower reactivity with the other polymers thus resulting in the removal of the first polymer by leaching. Applicant's method requires all other polymers to be inert, have a lower rate of reaction to the solvent or have a lower dissolution rate. Applicants' method relies on having different ratios of polymers in different regions of the scaffold in order for different porosity to result from the leaching. However, no claim claims a scaffold having different ratios of polymers in different regions. Applicants' specification also teaches that

> Alternatively or additionally, the leaching process may be controlled so that the leaching will be of a greater extent at the surface of the scaffold, and of a lesser extent at the core 14 of the scaffold 10. This may be by controlling the rate of immersion of the scaffold 10 in a bath of the solvent, controlling the time of immersion so that the solvent will not fully complete the dissolving of the first polymer nearer the core, or otherwise. As leaching will start at the surface of the scaffold 10 and progress towards the core 14 through the pores 12 created by leaching, by controlling the duration, temperature and agitation of the solvent bath, the core 14 may be only partially leached, or there may be no leaching at the core 14 of the scaffold 10. In this way the pores 12 will reduce in number, size and connectivity from the surface 22 of the scaffold 10 to the core 14 of the scaffold 10.

Applicants' specification, page 5, last paragraph to page 6, line 2. Applicants' method is the same or similar to the method (immersion) used by Isotis:

> In order to obtain the porous body, it is preferred that after subjecting the

> body to heat and/or pressure, the soluble particles are removed. One highly suitable way of doing this, is by submerging the body with the soluble particles in demineralized water or another suitable, non-toxic solvent in which the copolymer essentially does not dissolve, to allow the particles to dissolve. It is preferred to treat the water with UV prior to using it for dissolving the particles. Generally, it will be desired to repeat this procedure in demineralized water to achieve a substantially complete removal of the soluble particles. Once the soluble particles have been removed to a sufficient extent, the body may be dried, preferably slowly and under ambient conditions.

Isotis, page 9. Both depend on immersion to remove the particles.

6. Applicants argue

> Thus, Phipps discloses a process for complete removal of a leachant, and does not disclose or suggest ultrasonic leaching to provide controlled differential leaching of a first polymer at the surface and core.

In reply, Agrawal is newly cited for teaching methods of leaching (using ultrasonic vibration) to obtain gradients in porosity. Agrawal discloses implants having the claimed greater porosity at the surface and less porosity at the core.

7. Applicants argue that Shikinami and Hossainy do not cure the deficiency of Isotis, Brosnahan and Phipps. However, Agrawal is newly cited and discloses implants having the claimed greater porosity at the surface and less porosity at the core. Shikinami and Hossainy are cited for reasons as stated above.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUZANNE ZISKA whose telephone number is (571)272-8997. The examiner can normally be reached on Monday through Friday 9 AM to 5 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Blanchard can be reached on (571) 272-0827. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SUZANNE ZISKA/
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